

Exhibit 1

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Cover art: Rolando Corujo. A computer-generated representation of *p*-toluenesulfonyl chloride (see p. 466).
In this representation, carbon is black, hydrogen is white, chlorine is green, oxygen is red, and sulfur is yellow.

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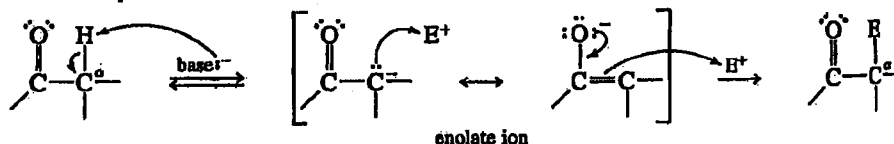
CHAPTER 22

Alpha Substitutions and Condensations of Enols and Enolate Ions

22-1 Introduction

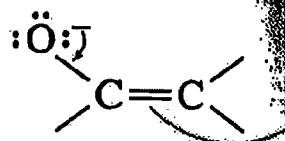
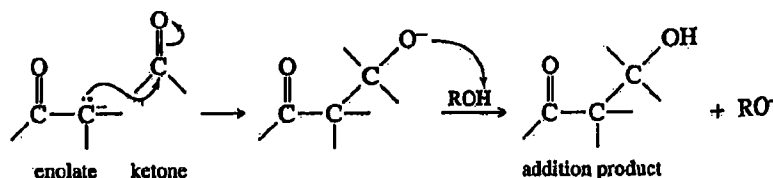
Up to now, we have studied two of the main types of carbonyl reactions: nucleophilic addition and nucleophilic acyl substitution. In these reactions, the carbonyl group serves as an *electrophile* by accepting electrons from an attacking nucleophile. In this chapter, we consider two more types of reactions: substitution at the carbon atom next to the carbonyl group (called alpha substitution) and carbonyl condensations. Alpha (α) substitutions involve the replacement of a hydrogen atom at the α carbon atom (the carbon next to the carbonyl) by some other group. Alpha substitution generally takes place when the carbonyl compound is converted to its enolate ion or enol tautomer. Both of these have lost a hydrogen atom at the alpha position, and both are *nucleophilic*. Attack on an electrophile completes the substitution.

Alpha substitution

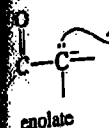


Carbonyl condensations are alpha substitutions where the electrophile is another carbonyl compound. From the electrophile's point of view, the condensation is either a nucleophilic addition or a nucleophilic acyl substitution. With ketones and aldehydes, protonation of the alkoxide gives the product of nucleophilic addition. With esters, loss of alkoxide gives the product of nucleophilic acyl substitution.

Condensation: Addition to ketones and aldehydes



Condensation: S

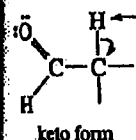


Alpha substitution is common. Many useful reactions can be carried out by considering

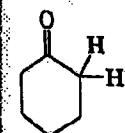
22-2A Keto

In the presence of a base, the negative charge on the alpha carbon can occur either by the loss of a hydrogen atom or by the loss of a vinyl group.

Base-catalyzed



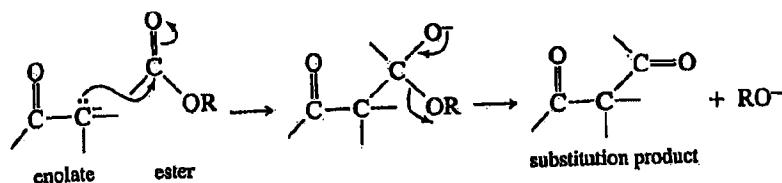
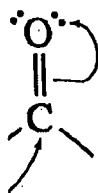
In this case, the keto form predominates. The enolate ion is formed by the loss of a hydrogen atom from the alpha carbon.



keto form (99.98%)

This type of movement of electrons is common in many reactions. Tautomers are different forms of the same molecule, differing only in the position of the double bond and the location of the hydrogen atom.

Condensation: Substitution with esters

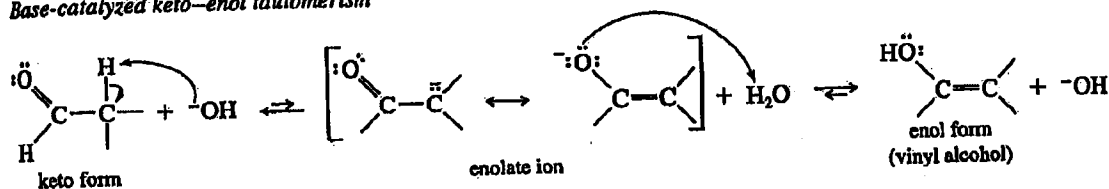


Alpha substitutions and condensations of carbonyl compounds are some of the most common methods for forming carbon-carbon bonds. A wide variety of compounds can participate as nucleophiles or electrophiles (or both) in these reactions, and many useful products can be synthesized. We begin our study of these reactions by considering the structure and formation of enols and enolate ions.

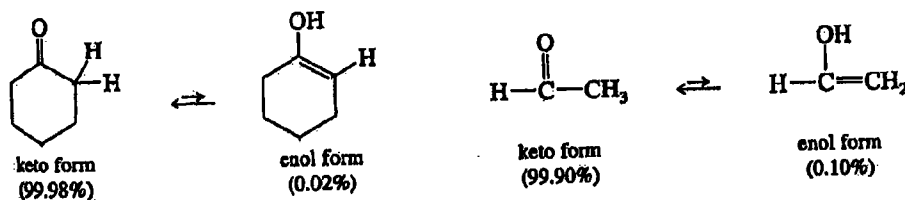
22-2A Keto-Enol Tautomerism

In the presence of strong bases, ketones and aldehydes act as weak proton acids. A proton on the α carbon is abstracted to form a resonance-stabilized enolate ion with the negative charge spread over a carbon atom and an oxygen atom. Reprotonation can occur either on the α carbon (returning to the keto form) or on the oxygen atom, giving a vinyl alcohol, the enol form.

Base-catalyzed keto-enol tautomerism



In this way, base catalyzes an equilibrium between isomeric keto and enol forms of a carbonyl compound. For simple ketones and aldehydes, the keto form predominates. Therefore, a vinyl alcohol (an enol) is best described as an alternative isomeric form of a ketone or aldehyde. In Section 9-9, we saw that an enol intermediate, formed by hydrolysis of an alkyne, quickly isomerizes to its keto form.

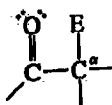


This type of isomerization, occurring by the migration of a proton and the movement of a double bond, is called **tautomerism**, and the isomers that interconvert are called **tautomers**. Don't confuse tautomers with resonance forms. Tautomers are true isomers (different compounds) with their atoms arranged differently. Under the right circumstances, with no catalyst present, either individual tautomeric form may be isolated. Resonance forms are different representations of the *same* structure, with all the atoms in the same places, showing how the electrons are delocalized.

22-2

Enols and Enolate Ions

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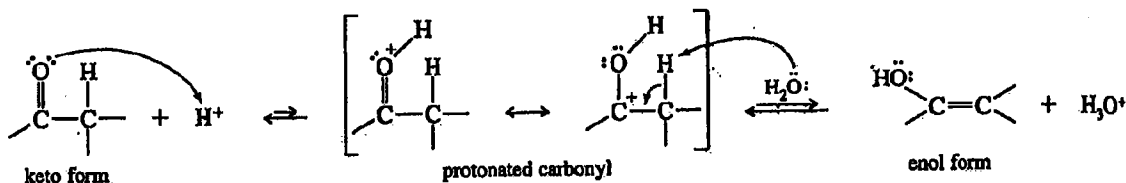


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Keto-enol tautomerism is also catalyzed by acid. In acid, a proton is moved from the α carbon to oxygen by first protonating oxygen and then removing a proton from carbon.

Acid-catalyzed keto-enol tautomerism

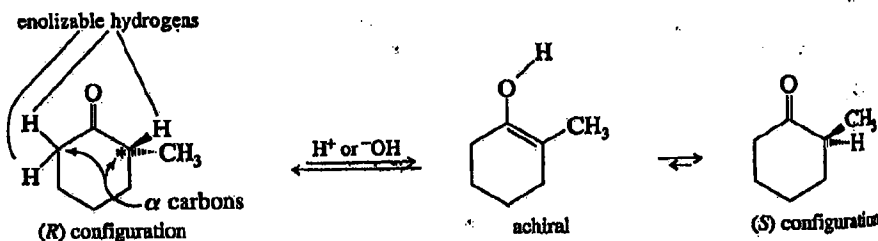


PROBLEM-SOLVING HINT

In acid, proton transfers usually occur by adding a proton in the new position, then deprotonating the old position; in base, by deprotonating the old position, then re-protonating at the new position.

Compare the base-catalyzed and acid-catalyzed mechanisms shown above for keto-enol tautomerism. In base, the proton is removed from carbon, then replaced on oxygen. In acid, oxygen is protonated first, then carbon is deprotonated. Most proton-transfer mechanisms work this way. In base, the proton is removed from the old location, then replaced at the new location. In acid, protonation occurs at the new location, followed by deprotonation at the old location.

In addition to its mechanistic importance, keto-enol tautomerism affects the stereochemistry of ketones and aldehydes. A hydrogen atom on an α carbon may be lost and regained through keto-enol tautomerism; such a hydrogen is said to be enolizable. If a chiral carbon has an enolizable hydrogen atom, a trace of acid or base allows that carbon to invert its configuration, with the enol serving as the intermediate. A racemic mixture (or an equilibrium mixture of diastereomers) is the result.



PROBLEM 22-1

Phenylacetone can form two different enols.

- Show the structures of these enols.
- Predict which enol will be present in the larger concentration at equilibrium.
- Give mechanisms for the formation of the two enols in acid and in base.

PROBLEM 22-2

Show each step in the mechanism of the acid-catalyzed interconversion of (*R*)- and (*S*)-2-methylcyclohexanone.

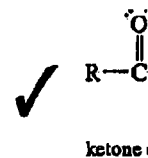
PROBLEM 22-3

When *cis*-2,4-dimethylcyclohexanone is dissolved in aqueous ethanol containing a trace of NaOH, a mixture of *cis* and *trans* isomers results. Give a mechanism for this isomerization.

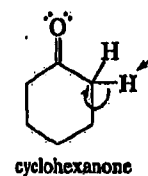
22-2B Formation and Stability of Enolate Ions

A carbonyl group dramatically increases the acidity of the protons on the α -carbon atom because most of the enolate ion's negative charge resides on the electronegative oxygen atom. The pK_a for removal of an α proton from a typical ketone

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Example



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PROBLEM

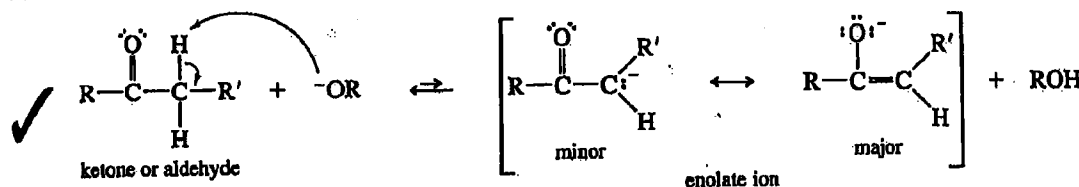
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or aldehyde is about 20, showing that a typical ketone or aldehyde is much more acidic than an alkane or an alkene ($pK_a > 40$), or even an alkyne ($pK_a = 25$). Still, a ketone or aldehyde is less acidic than water ($pK_a = 15.7$) or an alcohol ($pK_a = 16$ to 19). When a simple ketone or aldehyde is treated with hydroxide ion or an alkoxide ion, the equilibrium mixture contains only a small fraction of the deprotonated, enolate form.

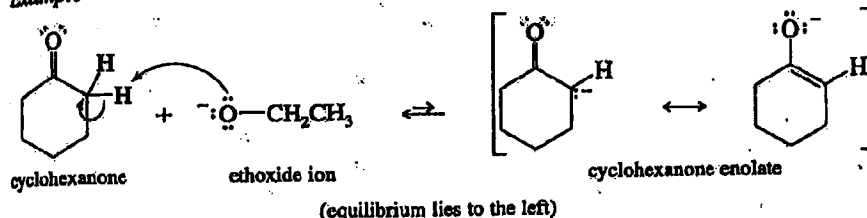
+ H_2O



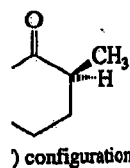
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Example



Even though the equilibrium concentration of the enolate ion may be small, it serves as a useful, reactive nucleophile. When an enolate reacts with an electrophile (other than a proton), the enolate concentration decreases, and the equilibrium shifts to the right (Fig. 22-1). Eventually, all the carbonyl compound reacts via a low concentration of the enolate ion.

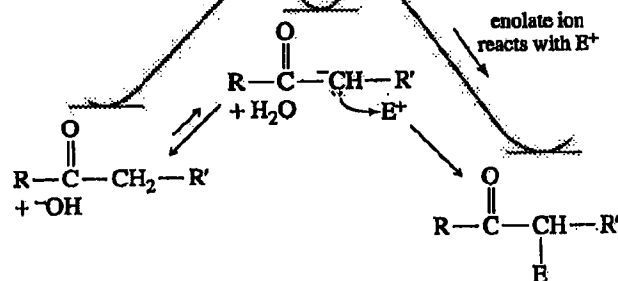


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?(R)- and (S)-

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◀ Figure 22-1
Reaction of the enolate ion
with an electrophile removes it
from equilibrium.

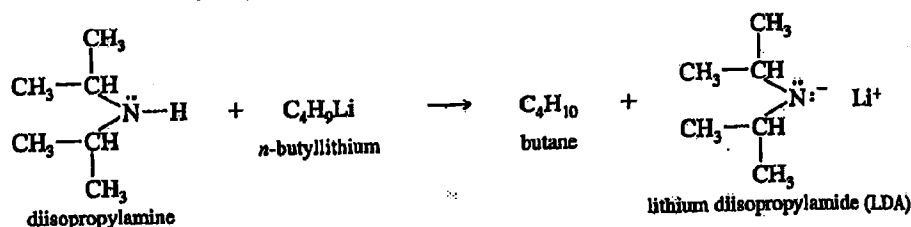
PROBLEM 22-4

Give the important resonance forms for the enolate ion of

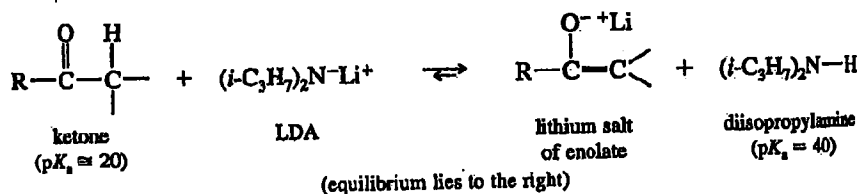
- (a) acetone (b) cyclopentanone (c) 2,4-pentanedione

Sometimes this equilibrium mixture of enolate and base won't work, usually because the base (hydroxide or alkoxide) reacts with the electrophile faster than the enolate does. In these cases, we need a base that reacts completely to convert the carbonyl compound to its enolate before adding the electrophile. Although sodium hydroxide

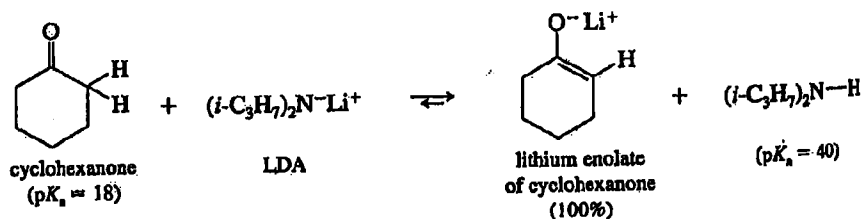
and alkoxides are not sufficiently basic, powerful bases are available to convert a carbonyl compound completely to its enolate. The most effective and useful base for this purpose is lithium diisopropylamide (LDA), the lithium salt of diisopropylamine. LDA is made by using an alkyllithium reagent to deprotonate diisopropylamine.



Diisopropylamine has a $\text{p}K_a$ of about 40, showing that it is much *less* acidic than a typical ketone or aldehyde. By virtue of its two isopropyl groups, LDA is a bulky reagent; it does not easily attack a carbon atom or add to a carbonyl group. Thus it is a powerful base, but not a strong nucleophile. When LDA reacts with a ketone, it abstracts the α proton to form the lithium salt of the enolate. We will see that these lithium enolate salts are very useful in synthesis.



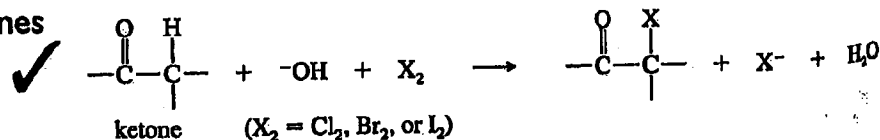
Example



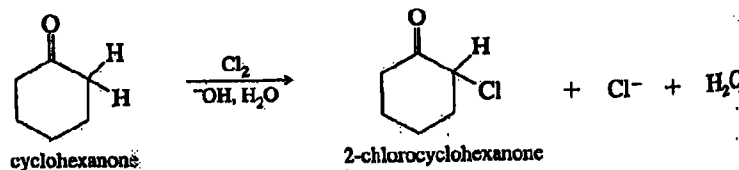
22-3 22-3A Base-Promoted α Halogenation

Alpha Halogenation of Ketones

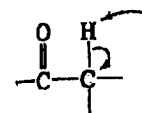
When a ketone is treated with a halogen and base, an α -halogenation reaction occurs.



Example



The base enolate ion on a ketone and:



This reacts as the equivalent of the

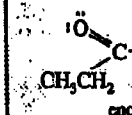
SOLVED PROBLEM

Propose a mechanism to give 2-bromocyclohexanone.

SOLUTION
In the presence of LDA:



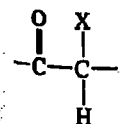
The enolate reacts with LDA:



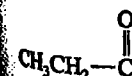
PROBLEM

Propose a mechanism.

Multiple Halogenation
With replacement of active toward withdrawing has



For example, after one halogenation, the carbonyl carbon is more reactive than the α carbon atom as the



monobrominated